REMARKS/ARGUMENTS

Status

Claims 67, 69-73 and 75-87 are under examination.

Claims 67, 70 and 73 are amended to refer to biological elements suspended in solution. Support is replete in the specification, which describes biological samples of cells and viruses introduced into a microfluidic device including, e.g., paragraph 0341 (harvested cells suspended in PBS), 0342 (cell suspension), 0276 (samples from environment which may be diluted), and 0316 (introduction of sample and buffer), referring to the paragraph numbering used in US 2005/0053952. Claims 67, 70 and 73 also recite that the biological element(s) are combined with a lysis chemical to release nucleic acids. Support is replete in the specification including, e.g., original claim 1 and paragraphs 0009, 0284, 0345, 0360, 0285, 0286, 0290, 0288, 0318, 0332, 0339, 0340, 0345, 0347, 0348, 0363. In Claims 76, 80 and 84 the term “lysing chemical” is replaced by “lysis chemical” solely for consistency. (“Lysis chemical”, “lysing chemical”, and “lysis solution” are used interchangeably in the specification.)

Interview

Applicants thank Examiner Calamita and SPE Gary Benzion for the courtesy of an interview at the patent office on March 16, 2010.

Rejections Under 35 USC 103(a)

Claims 67, 69, 76, 77, 78 and 79 were rejected under 35 U.S.C. 103(a) as allegedly obvious in view of US Pat. No. 6,007,690 ["Nelson"] and US Pat. No. 6,408,878 ["Unger"]

The methods of the invention application differ in numerous respects from those described in Nelson and Unger. *Inter alia*, the invention includes the step of physically isolating biological element(s) from a sample, by allowing the biological element(s) to flow past a first valve in a microfluidic flow channel of a microfluidic device, and creating a segment within the flow channel by actuating the first valve and a second valve, thereby trapping the biological element(s) in the segment.

In contrast, the Nelson reference described transporting a sample through an enrichment channel with a solid phase extraction (SPE) element. The SPE binds to a target analyte or subpopulation of cells, such that the target, but not unbound cells, is immobilized (*see* Nelson, Col. 5 and 6).

Applicants have explained in the amendment filed August 19, 2009, why the Office reasoning is incorrect. The remarks in the prior amendment are hereby incorporated by reference. To advance prosecution, Applicants now address the Office comments in the *Response to Applicant's Arguments.* In addition, independent claims 67, 70 and 73 have been amended to increase clarity. It is believed that in view of these remarks and amendments the claims are allowable.

Office Response to Applicant's Arguments

In the *Response to Applicant's Arguments* the Office states: "**Applicants argue [that in the method of] the instant invention cells are not selected based on binding of an antiligand or affinity to a matrix but rather by partition in a microfluidic channel. This argument is not persuasive because Applicants use the language of comprising therefore additional elements can be present in the prior art.**"

As Applicants understand that by "therefore additional elements can be present in the prior art", the Office is arguing that because the instant claims do not *exclude* an element (e.g., a solid phase extraction element), prior art (Nelson) containing the non-excluded element may be properly relied on by the Office.

Applicants do not disagree, but the issue here is not whether the prior art may include additional elements not found in the claims. The issue is whether the prior art teaches or suggests the steps or elements that are found in the claims. If claimed steps or elements are not found in or suggested by the prior art the Office cannot find the claim obvious. In this case, Nelson and Unger, taken together, did not suggest the present invention, including the step of physically isolating a biological element by allowing the element to flow past a first valve in a microfluidic channel, and creating a segment within the channel by actuating the first valve and a second valve of the microfluidic device.

The Office further states: "**Nelson teach separation in a microfluidic channel using anti-ligand or affinity to a matrix. . . . Unger et al. is relied on for and discloses the use of valves in microfluidic devices.**" As Applicants understand it, it is not disputed that Nelson neither described nor suggested physically isolating an individual biological element or a subset of the biological elements of a sample by partition within a microfluidic flow channel and Unger is relied on to remedy this deficiency.

Applicants agree that Unger, and many other prior art references, described microfluidic valves. Unger teaches that valves and pumps may be used as a substitute for electro-osmotic flow systems to transport fluid. However, the Office has not explained why one of skill reading Unger would have been motivated to *modify the method of Nelson*. Applicants submit there is no suggestion or reason to make such a modification. Clearly, the Office cannot argue that one of skill reading Unger would have *replaced* Nelson's SPE with valves. The basic principal of operation of the Nelson method requires binding of elements of interest in a solid phase extraction (SPE) chamber. It is well established that if a proposed modification of the prior art teaching would change the principle of operation of the prior art method, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Likewise, there can be no motivation for a modification of the prior art that renders the prior art invention unsatisfactory for its intended purpose. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). In this case the intended purpose of the SPE and method is to isolate cells based on binding properties. See MPEP 2143.01.

If, on the other hand, the Office intends to argue that one of skill would have modified Nelson by allowing cells to be bound by the SPE element, and then actuated valves to isolate the SPE element *after* cells were bound, Applicants disagree. First, such a modification would be fundamentally incompatible with the method of Nelson, which requires wash liquids to flow through the SPE-containing enrichment channel removing unbound elements, followed by elution liquids to remove bound elements. Second, *even if* the Nelson method was modified to valve-off the SPE element after the biological elements were bound, this would not constitute, physically isolating an individual biological element by actuating the valves, as claimed. In this scenario, any physical isolation in Nelson would have occurred prior to closing any hypothetical valves, during the binding step.

Third, to expedite prosecution Applicants have amended independent claims 67, 70 and 73 to recite that the biological elements are "suspended in a solution" in the segment. This is in contrast to Nelson, in which the basis of isolation is immobilization of the biological elements.

The Office also states, "**Applicants argue Nelson do not teach the biological elements may include combinations of cells that do not share a particular characteristic ligand recognized by a binding agent. This argument is not persuasive as Applicants are arguing limitations not currently recited in the instant claim.**" The Office has misunderstood Applicant's argument. The fundamental differences between the Nelson method and the present invention are fully captured in the claims. As a consequence of those differences, the Nelson device cannot accomplish what is accomplished by the present invention (and vice versa). The Nelson method involves selecting biological elements based on shared properties, which must be determined in advance in order to carry out the method. The claimed method does not involve selecting biological elements based on shared properties determined in advance. In short, the Nelson method and the claimed invention use fundamentally different approaches and, as a consequence, achieve fundamentally different results. No motivation is found in Unger's teaching of channels, valves, pumps, flow systems, or substitutes for electro-osmotic flow, to fundamentally modify the Nelson method to make it produce something other than its intended product.

For the reasons explained in the amendment filed August 19, 2009, and those above, the invention was not obvious in view of the cited references, and this rejection should be withdrawn.

Claims 70-73, 75, 80, 83, 84 and 87 were rejected over Nelson and Unger taken with Burlage. Nothing in Burlage remedies the deficiencies discussed above. Applicants note that Burlage paragraphs 0010, 0017, 0035, and 0065, cited by the Office, describe isolating cells using labeled nucleic acid probes and fluorescence-activated cell sorting, and have no relevance at all to the present invention.

Finally, with respect to claims 76,80, and 84, which recite a "cross-flow injector" the *Response to Applicant's Arguments* states "**Unger is relied on for the 'cross-flow injector.' Unger teaches using micropumps. A pump is the same thing as an injector.**" Applicants respectfully advise the Office that a pump is not the same thing as an injector, and particularly is not the same as a "cross-flow injector." A cross-flow injector is a configuration of channels and valves, such as illustrated in Fig. 20A-D, that allows a channel portion to be filled with a slug of fluid from one channel source, and expelled from the channel portion using a fluid from a different channel source. See the specification at paragraphs 0212-0217. With regard to Claim 87, the Office Action states Unger discloses "lysis in a rotary mixer," but, as in the first Office Action in this application, the Office does not explain where such a disclosure is found in the reference. Should any rejection be maintained, Applicants respectfully request clarification.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-462-5330.

Respectfully submitted,

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